https://rijournals.com/biological-and-applied-science/

RESEARCH INVENTION JOURNAL OF BIOLOGICAL AND APPLIED SCIENCES 2(1):6-9, 2023

©RIJBAS Publications ISSN: 1597-2879

Understanding the Role of Gut Microbiota-Derived Metabolites in Modulating Immune Responses

Okafor, Azubuike Ikechukwu

Department of Medical Biochemistry, University of Cross River State, Calabar, Nigeria
Email: okafor.azubuike@gmail.com; phone number: +2348035723454

ABSTRACT

Gut microbiota-derived metabolites play a critical role in modulating immune responses, impacting both local mucosal and systemic immunity. The complex interactions between the host immune system and microbial metabolites have evolved to maintain homeostasis and protect against pathogens. Dysbiosis, or disruption of the gut microbiota, is linked to various non-communicable diseases, such as diabetes, obesity, and cancer, often through immune dysregulation. This review explores the composition of gut microbiota, the metabolites they produce, and their impact on immune cells, including T cells, dendritic cells, and B cells. The clinical implications of these interactions are discussed, highlighting the potential for personalized therapies targeting gut microbiota-derived metabolites to treat immune-related diseases.

Keywords: Gut microbiota, metabolites, immune responses, dysbiosis, non-communicable diseases.

INTRODUCTION

The evolution of vertebrate-microbiome interactions is presumed to require co-evolution of microbiota and host immune systems, ensuring environmental molecular structures and microbes would be adequately recognized by the appropriate immune mechanism. Microbiota-derived metabolites are paramount in deciphering such interactions. Numerous compounds produced from the microbiota were shown to evoke protective or pathogenic immune responses to prevent pathogens' invasion or malignant outgrowth in a site-adapted manner. Remarkably, their effects have been intensively explored in various models of local mucosal or systemic immunity. However, potential unrelated endogenous compounds providing immune homeostasis were merely proposed. Illustrating the role of the microbiome as an evolutionary conduit for introducing immune-modulatory structural features is crucial for further understanding host-microbial interactions [1, 2, 3, 2, 4]. Non-communicable diseases such as diabetes, atherosclerosis, colonic cancer, and obesity are associated with alterations in intestinal microbiota. Such dysbiosis has an immune outcome, including increased intestinal permeability, enhanced low-grade inflammation, and broadened effector T cell functions outside the gut, contributing to the instigation and progression of systemic diseases. Recent findings highlighted that certain microbiota-derived metabolites or their metabolites exert beneficial health benefits by promoting peripheral and intraglandular accumulation of regulatory T cells and gut homing to maintain gut and systemic immune homeostasis. These metabolites are recognized by the respective receptors expressed in T cells, dendritic cells, or gut-homing B cells. Investigating the metabolism of these metabolites in various gut microorganisms associated with health and diseases will unveil the mechanisms of microbial modulation of immune homeostasis and provide insights into therapeutic approaches and preventive regimes by manipulating gut microbiota and metabolites [5, 6, 7, 8].

GUT MICROBIOTA COMPOSITION AND METABOLITES

The gut microbiota is composed of diverse microorganisms, including bacteria, archaea, fungi, viruses, and phages, that colonize the mammalian gastrointestinal tract in the early stages of life and evolve with age. The gut microbiota maintains a comensal relationship with the host and participates in the metabolism of food and energy. It also regulates the transcription of host genes and the expression of various proteins, thereby impacting immune response and homeostasis. In addition to the gut, microbiota are also found in various human tissues and organs, including the skin, respiratory tract, and liver. The maintenance of microbial community structure is tightly associated with health status, and alteration of

gut microbiota can result in the occurrence and development of many human diseases [9, 10, 11]. The gut microbiota produces a broad range of microbiota-derived metabolites, which are mainly derived from dietary substrates, host-derived molecules, or absorbed compounds. The gut microbiota possesses unique enzymatic capabilities to transform dietary molecules that are not convertible by host enzymes or convert bioactive molecules that are extensively modified after absorption and circulation, resulting in metabolite production. Gut microbiota-derived metabolites include small molecules and macromolecules and exert profound effects on the host by serving as ligands for different receptors to stimulate downstream effects [12, 13, 14].

IMMUNE SYSTEM: AN OVERVIEW

The immune system consists of a network of cells and proteins that defend the body against infection. The cells and tissues of the immune system are distributed widely throughout the body. The immune system has two principal components: the innate immune system and the adaptive immune system. The innate immune system acts as a first line of defense against pathogens and is required for the initiation and development of adaptive immune responses. The adaptive immune response acts as a highly specific second line of defense and functions to eliminate pathogens that have escaped the innate immune response. Although it is prevalent to consider the immune system as one single entity, the innate immune system and the adaptive immune system each have their own specialized cells and tissues. The potential routes of immune system interaction with gut microbiota are highlighted, while the roles of gut microbiota-derived metabolites in mammalian immunity are investigated [15, 16, 17]. The gut microbiota is a complex ecosystem that regulates host health and physiology. Microbiota-derived metabolites, including the short-chain fatty acids acetate, propionate, and butyrate, bile acid metabolites, and tryptophan metabolites such as indole and serotonin, are essential for maintaining gut and systemic immune homeostasis. Gut-microbiota-derived metabolites enhance the intestinal physical barrier and maintain mucosal immune tolerance via G protein-coupled receptors or epigenetic mechanisms. In addition, they also promote Treg, M2 macrophages, and M2-like macrophages differentiation, inhibit the activation of Th1, Th2, Th17, and inflammatory macrophages, and modulate the function of DCs, thereby preventing excessive immune responses and inflammation. Dysbiosis-derived metabolites induce the differentiation of effector T cells, inflammatory macrophages, and Th9 cells, enhance IgE and IgG production by B cells, and promote mast cell degranulation, which initiates the occurrence and development of allergic diseases. As the structure of gut microbiota and the composition of metabolites differ significantly between individuals, personalized therapy targeting gut microbiota-derived metabolites holds great promise for the prevention and treatment of diseases related to immune dysfunction [18, 19, 20].

INTERACTIONS BETWEEN GUT METABOLITES AND IMMUNE RESPONSES

Gut microbiota intercommunicates with the mucosal immune system primarily through its metabolites to maintain immunological homeostasis. These microbial metabolites impact the immune system and ameliorate various disorders, including metabolic disease and autism spectrum disorder. Short-chain fatty acids (SCFAs), bile acids (BAs), and polyamines, are known to mediate the interactions between gut metabolomes and mucosal immunobiomes. Gut microbiota-derived microbial metabolites regulate the immune system, including differentiation and activation of immune populations, immune tolerance, modulation of innate and adaptive immune responses, and promotion or inhibition of pathological immune responses in diverse diseases [21, 22, 23]. Among the various microbial metabolites, accumulating evidence has focused on the immune-modulatory function of SCFAs, BAs, and polyamines by activating receptor-mediated pathways. The activities of SCFA and BA metabolites are mediated through various receptors including free fatty acid receptors (FFARs1, FFAR2, and FFAR3), G protein-coupled receptors (GPCRs), G-protein-coupled bile acid receptor 1 (GPBAR1), and MRGPRD. Polyamines such as spermine, spermidine, and putrescine regulate the metabolic pathways in immune populations, impacting the host health and disease status [24, 25, 26].

CLINICAL IMPLICATIONS AND THERAPEUTIC POTENTIAL

Understanding the intricate interplay between gut microbiota-derived metabolites and immune responses can have practical applications, ranging from the design of novel probiotics to the stratification of patients in microbiome-based therapeutic approaches. The current advances in profiling and modulation of microbiome signatures open new doors for predictive and personalized medicine. Advances in our understanding of gut microbiota-derived metabolites and their role in modulating immune responses can have a significant impact on various health conditions. It can aid in the design of novel probiotic strains or food ingredients with tailored functional properties. Modulatory potential on immune response, including both pro-inflammatory and anti-inflammatory potential, could be used as a criterion for selecting strains

or ingredients to be included in food products. In reciprocal studies, complex food products could be screened for their modulatory potential on inflammatory markers using in vitro models, offering the possibility to identify food ingredients that positively affect gut health [27, 2, 28]. Screening of monocultures derived from the gut microbiota could also uncover metabolite signatures suitable for modulating immune responses from the host's perspective. Beyond bacterial strains, this knowledge could contribute to the selection of specific types or sources of fiber-containing food ingredients that steer the fermentation pattern towards the production of beneficial immunomodulatory metabolites. This information could be further validated in clinical studies, where the modulation of gut microbiota-derived metabolites is monitored in parallel with the amelioration of diseases or health conditions linked to dysregulation of immune responses. Additionally, multi-omic profiling with metadata on health outcomes or systematic stratification of disease and control cohorts could provide further insights into beneficial metabolite signatures for personalized interventions. Furthermore, the growing knowledge on the modulation of microbiomic signatures opens the possibility of predicting immune outcomes by applying biostatic analysis on microbiome profiles earlier in life, before the onset of diseases. This approach could offer new opportunities for preventive strategies [27, 29, 2, 30].

CONCLUSION

Understanding the intricate relationship between gut microbiota-derived metabolites and immune responses provides valuable insights into the maintenance of immune homeostasis and the pathogenesis of various diseases. The modulation of gut microbiota and their metabolites offers promising therapeutic potential for treating immune-related disorders and preventing disease progression. Future research should focus on personalized approaches to manipulate these microbial metabolites, paving the way for novel treatments and preventive strategies in immune-mediated diseases.

REFERENCES

1. Wang J, Zhu N, Su X, Gao Y et al. Gut-microbiota-derived metabolites maintain gut and systemic immune homeostasis. Cells. 2023. mdpi.com
2. Feng W, Liu J, Cheng H, Zhang D, Tan Y, Peng C. Dietary compounds in modulation of gut microbiota-derived metabolites. Frontiers in Nutrition. 2022 Jul 19;9:939571. frontiersin.org
3. Luu M, Schütz B, Lauth M, Visekruna A. The impact of gut microbiota-derived metabolites on the tumor immune microenvironment. Cancers. 2023. mdpi.com
4. Jasim SA, Opulencia MJ, Ramírez-Coronel AA, Abdelbasset WK, Abed MH, Markov A, Al-Awsi GR, Shamsiev JA, Hammid AT, Shalaby MN, Karampoor S. The emerging role of microbiota-derived short-chain fatty acids in immunometabolism. International Immunopharmacology. 2022 Sep 1;110:108983. [HTML]
5. Behera SK, Praharaj AB, Chalikonda G, Srivani G, Mahapatra N. Gut Microbiota as Signatures in Non-communicable Diseases and Mucosal Immunity. Theranostics Approaches to Gastric and Colon Cancer. 2020:167-208. [HTML]
6. Tan J, Taitz J, Nanan R, Grau G, Macia L. Dysbiotic gut microbiota-derived metabolites and their role in non-communicable diseases. International Journal of Molecular Sciences. 2023 Oct 17;24(20):15256. mdpi.com
7. Hosseinkhani F, Heinken A, Thiele I, Lindenburg PW, Harms AC, Hankemeier T. The contribution of gut bacterial metabolites in the human immune signaling pathway of non-communicable diseases. Gut microbes. 2021 Jan 1;13(1):1882927. tandfonline.com
8. Shelton CD, Byndloss MX. Gut epithelial metabolism as a key driver of intestinal dysbiosis associated with noncommunicable diseases. Infection and Immunity. 2020. asm.org
9. Vernocchi P, Del Chierico F, Putignani L. Gut microbiota metabolism and interaction with food components. International Journal of Molecular Sciences. 2020 May 23;21(10):3688. mdpi.com
10. Cheng Z, Zhang L, Yang L, Chu H. The critical role of gut microbiota in obesity. Frontiers in endocrinology. 2022. frontiersin.org
11. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nature Reviews Microbiology. 2021. usp.br
12. Ahmed H, Leyrolle Q, Koistinen V, Kärkkäinen O, Layé S, Delzenne N, Hanhineva K. Microbiota-derived metabolites as drivers of gut–brain communication. Gut microbes. 2022 Dec 31;14(1):2102878. tandfonline.com
13. Hu Y, Chen Z, Xu C, Kan S et al. Disturbances of the gut microbiota and microbiota-derived metabolites in inflammatory bowel disease. Nutrients. 2022. mdpi.com
14. Zheng L, Wen XL, Duan SL. Role of metabolites derived from gut microbiota in inflammatory bowel disease. World Journal of Clinical Cases. 2022. nih.gov

15. Mapunda JA, Tibar H, Regragui W, Engelhardt B. How does the immune system enter the brain?. Frontiers in immunology. 2022 Feb 22;13:805657. frontiersin.org
16. Krishnamurty AT, Turley SJ. Lymph node stromal cells: cartographers of the immune system. Nature immunology. 2020. [HTML]
17. Suo C, Dann E, Goh I, Jardine L, Kleshchevnikov V, Park JE, Botting RA, Stephenson E, Engelbert J, Tuong ZK, Polanski K. Mapping the developing human immune system across organs. Science. 2022 May 12;376(6597):eabo0510. nih.gov
18. Ranjbar R, Vahdati SN, Tavakoli S, Khodaie R, Behboudi H. Immunomodulatory roles of microbiota-derived short-chain fatty acids in bacterial infections. Biomedicine & Pharmacotherapy. 2021 Sep 1;141:111817. sciencedirect.com
19. van der Hee B, Wells JM. Microbial regulation of host physiology by short-chain fatty acids. Trends in Microbiology. 2021. cell.com
20. Kim CH. Complex regulatory effects of gut microbial short-chain fatty acids on immune tolerance and autoimmunity. Cellular & molecular immunology. 2023. nature.com
21. Ohno H. The impact of metabolites derived from the gut microbiota on immune regulation and diseases. International Immunology. 2020. [HTML]
22. Su X, Gao Y, Yang R. Gut microbiota derived bile acid metabolites maintain the homeostasis of gut and systemic immunity. Frontiers in immunology. 2023. frontiersin.org
23. Li C, Liang Y, Qiao Y. Messengers from the gut: gut microbiota-derived metabolites on host regulation. Frontiers in Microbiology. 2022. frontiersin.org
24. Li X, Liu L, Cao Z, Li W, Li H, Lu C, Yang X, Liu Y. Gut microbiota as an "invisible organ" that modulates the function of drugs. Biomedicine & pharmacotherapy. 2020 Jan 1;121:109653. sciencedirect.com
25. Chen Y, Chen YX. Microbiota-associated metabolites and related immunoregulation in colorectal cancer. Cancers. 2021. mdpi.com
26. Manoharan N, Parasuraman R, Jayamurali D, Govindarajulu SN. The therapeutic role of microbial metabolites in human health and diseases. InRecent Advances and Future Perspectives of Microbial Metabolites 2023 Jan 1 (pp. 1-38). Academic Press. [HTML]
27. Yang W, Cong Y. Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases. Cellular & molecular immunology. 2021. nih.gov
28. Wei YX, Zheng KY, Wang YG. Gut microbiota-derived metabolites as key mucosal barrier modulators in obesity. World Journal of Gastroenterology. 2021. nih.gov
29. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nature reviews Gastroenterology & hepatology. 2020. unama.br
30. Caffaratti C, Plazy C, Mery G, Tidjani AR, Fiorini F, Thiroux S, Toussaint B, Hannani D, Le Gouellec A. What we know so far about the metabolite-mediated microbiota-intestinal immunity dialogue and how to hear the sound of this crosstalk. Metabolites. 2021 Jun 21;11(6):406. mdpi.com

CITE AS: Okafor, Azubuike Ikechukwu. Understanding the Role of Gut Microbiota-Derived Metabolites in Modulating Immune Responses. RESEARCH INVENTION JOURNAL OF BIOLOGICAL AND APPLIED SCIENCES. *2023 2(1):6-9.*